



North Carolina Department of Health and Human Services
Division of Public Health

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To: North Carolina Health Care Providers and Laboratories
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Subject: **Zika Virus Diagnosis, Management and Reporting (4 pages)**

This memo is intended to provide information to NC clinicians and laboratories regarding diagnosis, management and reporting of Zika virus infection.

This version has been updated to include revised guidance regarding consideration of serologic testing for asymptomatic pregnant women who traveled to areas with ongoing Zika virus transmission; new guidance regarding prevention measures; and updated guidance regarding specimen collection and shipment.

Summary

Zika is a mosquito-borne virus that is currently causing a large outbreak in Brazil, including reports of pregnant women giving birth to babies with birth defects. Zika virus was first identified in Uganda in 1947 and is transmitted by *Aedes aegypti* and *A. albopictus* mosquitos. Since 2007, Zika virus has caused large outbreaks in Gabon, Micronesia and French Polynesia. Since 2015, endemic transmission has been occurring in Central and South America. A map of countries and territories with active Zika virus transmission is available at <http://www.cdc.gov/zika/geo/index.html>.

To date, most cases identified in the continental United States have been among persons with recent travel to an area of ongoing transmission; one locally-acquired case in Texas was linked to sexual transmission.

Clinical and Epidemiologic Features

Approximately 1 in 5 people infected with Zika virus become ill. Symptoms begin about 3–12 days after exposure, last between 2 and 7 days and include mild fever, rash (mostly maculopapular), headaches, arthralgia, myalgia, and non-purulent conjunctivitis. Patients may remain viremic for up to 7 days after symptom onset. Clinical symptoms are often similar to dengue and chikungunya infections.

An increase in Guillain-Barré syndrome has been noted in some areas with active Zika virus transmission. Investigations are ongoing to determine whether Zika virus increases the risk of Guillain-Barré syndrome.

Isolated cases of Zika virus transmission through blood transfusion and sexual contact have been reported. Zika virus, like dengue, can be detected in saliva and urine. However, exposure to these fluids has not been linked to transmission.

Case management

Because of similar geographic distribution and symptoms, patients with suspected Zika virus infections also should be evaluated and managed for possible dengue or chikungunya infection. Similar to dengue and chikungunya infections, no specific antiviral treatment is available for Zika virus infection. Treatment is generally symptomatic and can include rest, fluids, and use of acetaminophen. Aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs), like ibuprofen and naproxen, should be avoided until dengue can be ruled out to reduce the risk of hemorrhage.

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Zika Virus Infection and Pregnancy

There have been reports of congenital microcephaly and other poor pregnancy outcomes in babies of mothers who were infected with Zika virus while pregnant. The link between Zika virus and these outcomes is still under investigation.

Health care providers should ask all pregnant women about recent travel. Pregnant women who develop symptoms consistent with Zika virus infection within two weeks of travel to an area with ongoing transmission should be evaluated by a health care provider and recommended for testing as described below. Serologic testing for Zika virus can also be offered to asymptomatic pregnant women 2–12 weeks after travel to areas with ongoing transmission.

CDC and the American Congress of Obstetricians and Gynecologists (ACOG) recommend that an ultrasound evaluation be performed for asymptomatic pregnant women reporting travel at any time during pregnancy to an area with ongoing transmission in order to detect fetal microcephaly or intracranial calcifications. Serial ultrasound screening (every 3–4 weeks) may be considered at the discretion of the provider.

Biparietal diameter and head circumference are used to detect microcephaly on ultrasound. Normally, these measurements are not used before 14 weeks gestation. There is limited information regarding timing or diagnostic accuracy of ultrasound for detection of fetal microcephaly or intracranial calcifications associated with Zika virus infection. Additional recommendations for management of pregnant women with travel history to an area with ongoing Zika virus transmission are available at <http://www.cdc.gov/zika/hc-providers/qa-pregnant-women.html> and <https://www.acog.org/About-ACOG/News-Room/Practice-Advisories/Practice-Advisory-Interim-Guidance-for-Care-of-Obstetric-Patients-During-a-Zika-Virus-Outbreak>.

Recommendations for additional assessment and laboratory testing for infants with possible congenital Zika virus infection are available at <http://www.cdc.gov/zika/hc-providers/qa-pediatrician.html>.

Prevention Measures

Travel advisory: Due to reports of microcephaly and other poor outcomes in babies of mothers who were infected with Zika virus while pregnant, the CDC recommends the following:

- Pregnant women should consider postponing travel to areas where Zika virus transmission is ongoing.
- Pregnant women and women trying to become pregnant who do travel to these areas should talk to their healthcare providers first and strictly follow steps to avoid mosquito bites during their trip.

Mosquito avoidance: The mosquitoes responsible for most Zika virus transmission are not believed to be widespread in North Carolina. However, persons being evaluated for Zika virus infection should still be advised to use personal protective measures to avoid exposure to mosquitoes during the first 7 days after symptom onset. These measures include:

- Avoiding outdoor exposure when mosquitoes are most active. The mosquitos that transmit Zika virus are aggressive daytime biters, so always use personal preventive measures to prevent bites at all times of day.
- Using personal preventive measures – i.e., wearing insect repellent and covering up: <http://www.cdc.gov/features/stopmosquitoes/>
- Reducing breeding sites for *Aedes* species mosquitoes in your yard: http://epi.publichealth.nc.gov/cd/arbo/mosquito_fs.pdf

Additional measures:

- Refrain from donating or selling any blood products until symptoms have resolved and until 28 days after travel to an area with ongoing transmission.
- Men who reside in or have traveled to an area of active Zika virus transmission who have a pregnant partner should abstain from sexual activity or consistently and correctly use condoms during sex (i.e., vaginal intercourse, anal intercourse, or fellatio) for the duration of the pregnancy.
- Men who reside in or have traveled to an area of active Zika virus transmission and have nonpregnant sex partners might consider abstaining from sexual activity or using condoms consistently and correctly during sex until more is known about persistence of virus in semen and factors associated with sexual transmission.

Laboratory Testing:

Testing for Zika virus should be conducted in consultation with the state and local public health for the following individuals:

Pregnant women

- Testing is recommended for pregnant women presenting with signs and symptoms consistent with Zika virus disease (acute onset of fever, maculopapular rash, arthralgia, or conjunctivitis) within two weeks of travel to an area with ongoing transmission.
- Testing is also recommended for asymptomatic pregnant women who have ultrasound findings of fetal microcephaly or intracranial calcifications and who report travel to an area with ongoing transmission during pregnancy.

- Serologic testing can be offered to asymptomatic pregnant women from 2–12 weeks after return from travel to areas of ongoing Zika virus transmission.

Non-pregnant persons

- Patients presenting with signs and symptoms consistent with Zika virus disease (acute onset of fever, maculopapular rash, arthralgia, or conjunctivitis) within two weeks of travel to an area with ongoing transmission.

Approval is required for submission of specimens. Please contact the Communicable Disease Branch at 919-733-3419 or your local health department to facilitate testing if Zika virus infection is suspected.

Testing methods

Because of concurrent circulation of Zika, dengue, and chikungunya viruses and the similarity of illness presentation, CDC recommends concurrent testing for all three viruses in patients with a recent history of travel to an affected area and clinically compatible illness.

Appropriate testing is determined based on how long after symptom onset the specimen is collected.

- Specimens collected <4 days after symptom onset will be subjected to molecular testing (RT-PCR) for all three viruses.
- Specimens collected 4–7 days after symptom onset will be subjected to molecular testing and serologic testing for virus-specific IgM antibodies. Because serum collected within 7 days of illness onset may not have detectable virus-specific IgM antibodies, IgM testing should be repeated on a convalescent-phase sample.
- Specimens collected >7 days after symptom onset and specimens from asymptomatic pregnant women collected 2–12 weeks after return from travel to areas of ongoing Zika virus transmission will be subjected to serologic testing for virus-specific IgM antibodies.

Where to test

Testing for Zika, dengue, and chikungunya viruses will be coordinated by the NC State Laboratory of Public Health (NCSLPH) and conducted in collaboration with CDC. The provider for each patient should complete the following forms:

- The NCSLPH submission form DHHS 3445, which is available at <http://slph.state.nc.us/virology-serology/special-serology.asp>. (At the bottom of this form, please check “Forward to CDC” and write in specific tests requested. NCSLPH will perform chikungunya molecular and serological testing with a 6 business day turn-around-time.)
- The CDC 50.34 DASH form, which is available at <http://slph.ncpublichealth.com/Forms/CDC-5034-DashForm-120515.pdf>. This form must be completed online and then printed. Be sure to use ‘Test Order Name’ as ‘Arbovirus Serology.’

Because of the extensive cross-reactivity between the Flaviviruses, **the following information must be provided with submitted specimens:**

- Travel history, onset date, specimen collection date, specimen type, description of clinical illness, vaccination history (specifically yellow fever and Japanese encephalitis vaccines), and submitter contact information.
- When submitting perinatal specimens or specimens collected from pregnant women, please include the gestational age of the fetus at the time of travel.

Submitters should also request testing for all three viruses on both test request forms. Both forms should be completed for all specimens, acute and convalescent, and should be submitted to the NC SLPH.

Table: specific specimen collection, testing, and shipment information for Zika, Chikungunya and Dengue Testing:

Specimen	Test Performed	Specimen Volume	Shipment
Serum	Chikungunya RT-PCR & IgM; Zika and Dengue RT-PCR and virus-specific IgM; Flavivirus PRNT	2–5 mL serum	Refrigerated (4°C), placed on cold packs if shipment is to be received within 72 hrs of collection. For delays exceeding 72 hrs, freeze at -70°C & ship on dry ice.

Urine	Zika RT-PCR	1–3 ml	Refrigerated (4°C), placed on cold packs if shipment is to be received within 72 hrs of collection. For delays exceeding 72 hrs, freeze at -70°C & ship on dry ice.
Amniotic Fluid*	Zika RT-PCR	0.5–3 ml	
Cord Blood	Zika RT-PCR & IgM; Flavivirus PRNT	0.5–3 ml	Refrigerated (4°C), placed on cold packs
Placental Tissue	Zika RT-PCR; Viral Culture	2–5 grams	Freeze at -70°C & ship on dry ice.
Placental Tissue and Umbilical Cord	Immunohistochemical Staining & Zika virus RT-PCR	2–5 grams of tissue and/or paraffin blocks	Tissue should be formalin-fixed or paraffin-embedded. Ship specimens at room temperature. Note: Request consultation with NCSLPH for specific instructions.

*Patient and healthcare provider must weigh risks and benefits of testing prior to collection of amniotic fluid.

Contact the NCSLPH at 919-807-8600 prior to any shipment or if you have questions. Specimen transport using the statewide courier can be coordinated with your local health department or specimens can be directly shipped to the NCSLPH using a professional courier service. All specimens should be packaged and shipped as a Category B infectious substance.

Address all specimen shipments as follows: Attention: Virology/Serology Unit
North Carolina State Laboratory of Public Health
4312 District Drive
Raleigh, NC 27607-5490

Surveillance and Reporting:

Physicians and laboratories are required to report suspected or confirmed Zika virus infections. Please contact the Communicable Disease Branch at 919-733-3419 or your local health department if Zika virus infection is suspected.

This is an evolving situation and recommendations are likely to change as new information becomes available. Updated information and guidance are available from CDC at <http://www.cdc.gov/zika>.